

## Evaluation of the Long-Term Survival in Non-Metastatic Young Breast Cancer Patients in South of Iran

Behnam Kadkhodaei<sup>1</sup> , Ahmad Mosalaei<sup>1</sup> , Shapour Omidvari<sup>3,1</sup> , Mansour Ansari<sup>3,1</sup> ,  
 Mohammad Mohammadianpanah<sup>2,1</sup> , Niloofar Ahmadloo<sup>3,1</sup> , Hamid Nasrollahi<sup>1</sup> ,  
 Seyed Hassan Hamed<sup>1</sup> , Mehdi Shariat<sup>3</sup> , Mozhdeh Zamani<sup>4\*</sup> 

1. Dept. of Radiation Oncology, Shiraz University of Medical Sciences, Shiraz, Iran
2. Colorectal Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
3. Breast Diseases Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
4. Autophagy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

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### Corresponding Information:

**Mozhdeh Zamani,**  
 Autophagy Research Center, Shiraz  
 University of Medical Sciences, Shiraz,  
 Iran

**E-Mail:**  
[mozhdeh.zamani63@gmail.com](mailto:mozhdeh.zamani63@gmail.com)  
[mozamani@sums.ac.ir](mailto:mozamani@sums.ac.ir)

### ABSTRACT

**Background & Objective:** The lack of breast cancer screening in young women leads to late disease diagnosis and worse outcomes in this age group. This study was designed to evaluate clinicopathological features and long-term outcomes of young breast cancer women in south of Iran.

**Materials & Methods:** This is a retrospective study of breast cancer patients who were pathologically diagnosed during 2005 to 2017. Data from 284 breast cancer patients aged 40 years or younger were included in this study. Demographic, clinicopathological properties as well as treatment modalities including type of surgery, adjuvant radiotherapy, and adjuvant or neoadjuvant chemotherapy were recorded and analyzed.

**Results:** Median age of the patients was 36 (range 23-40) years. After a median follow-up of 68 months, 21 patients had died due to the disease, 59 patients were alive with the disease, and 204 patients were alive without the disease. The univariate COX regression demonstrated that the disease-free survival (DFS) was significantly low in patients who had undergone breast conservation surgery (BCS) and also patients with higher stages, estrogen/progesterone-negative and human epidermal growth factor receptor 2-positive (ER-/PR-/HER2+) status. Low overall survival (OS) was also significantly associated with stage. According to multivariate COX regression, BCS, stages II, III and also young age were independent predictive factors for low DFS.

**Conclusion:** Given the aggressive features and worse outcome of young breast cancer patients, treatment remains tough and screening seems to be required at young age. Further studies are required to find best management and therapeutic protocols for these patients.

**Keywords:** Breast cancer, Young age, Overall survival, Disease-free survival



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## Introduction

Breast cancer is known as the most frequent cancer affecting women around the world particularly in developed countries (1,2). Although this cancer occurs more frequently in women over 50 years of age, recent increasing incidence rates of breast cancer in young women under 40 years of age attract particular attention (3). It has been estimated that about 7% and 4% of all diagnosed breast cancers are in women < 40 years and < 35 years, respectively (4). Due to low incidence in young age, breast cancer screening programs are not performed for these women, which unfortunately leads to late diagnosis of disease in the symptomatic phase with advanced stage (3,5). A large population-based study described some risk factors for breast cancer in

premenopausal women including combination of high caloric intake, obesity, sedentary lifestyle, and high alcohol and red meat consumption. Body mass index (BMI) is positively associated with high breast cancer risk in post-menopausal women (6,7). The incidence of breast cancer during pregnancy (BCP) has increased within the last few decades. The postponing of childbearing and high maternal age in developed and also several developing countries lead to the increase of the BCP cases (8,9). Previous estimations show that about 10-20% of breast cancers in 30-year-olds or younger women are recognized either within pregnancy or during the first year after delivery (10,11). Since young patients are at higher risk due to their age, adjuvant therapies should be

considered within treatment management. However, there are several long-term side effects like early menopause induction, fertility defects, reduction of bone mineral density and development of secondary malignancy due to chemotherapy and radiotherapy (12-14). Although breast cancer is relatively uncommon in young women, it is considered a remarkable clinical concern due to its worse clinical outcome. The goal of this study was to evaluate the clinicopathological characteristics and long-term clinical outcomes of young breast cancer women in Shiraz, Iran.

## Materials and Methods

### Study design and data collection

This study was designed as a retrospective study of breast cancer patients who were pathologically diagnosed during 2005 to 2017 and treated at the Radiotherapy and Oncology Center of Namazi Hospital in Shiraz, as a referral center in the south of Iran. Finally, data from 284 breast cancer patients who were 40 years old or younger were included in this study. The baseline demographic and clinicopathological features including age, hormone receptors status (Estrogen Receptor (ER), Progesterone Receptor (PR) and the human epidermal growth factor receptor 2 (HER-2) receptor), histological type, stage, T and N stages, grade, operation type, relapse, the presence of lymphovascular invasion (LVI), chemotherapy timing,

and adjuvant radiotherapy were recorded and analyzed. The minimum and maximum follow-up of patients were 36 and 156 months for patients who were pathologically diagnosed in 2017 and 2005, respectively.

### Statistical analysis

SPSS version 20 (SPSS Inc., Chicago, IL, USA) was applied for data analysis. Disease-free survival (DFS) and overall survival (OS) were analyzed using the Kaplan-Meier (KM) estimation method. Both univariate and multivariate Cox regression analyses were applied in order to identify the independent predictive variables for survival. The *P* values less than 0.05 were considered to be statistically significant.

### Ethical Considerations

Ethical approval for the study was obtained from the Institutional Ethics Committee of Shiraz University of Medical Sciences (SUMS) according to the Helsinki declaration (Ethic code: IR.SUMS.MED.REC.1397.232). All patients were informed about the aim of the study and asked to complete the informed consent form.

## Results

The baseline demographic and clinicopathological characteristics of the young breast cancer patients are demonstrated in [Table 1](#).

**Table 1.** Baseline characteristics of young breast cancer patients

Characteristics	Number of Patients (%)
<b>Categorized age in years</b>	
20 to 25	16(5.6)
26 to 30	30 (10.6)
31 to 35	85(29.9)
36 to 40	153(53.9)
<b>Hormone Reseptor Status</b>	
ER+,PR+,HER2-	166(58.5)
ER-,PR-,HER2+	26(9.2)
ER+,PR+,HER2+	39(13.7)
ER-,PR-,HER2-	49(17.3)
Missing/unknown	4(1.4)
<b>Histological type</b>	
Ductal	270(95.1)
Lobular	6(2.1)
Medullary	7(2.5)
Papillary	1(0.4)
<b>Stage</b>	
I	59 (20.8)
II	160 (56.3)
III	65(22.9)

Characteristics	Number of Patients (%)
<b>T stage</b>	
T1	66 (23.2)
T2	175 (61.6)
T3	40 (14.1)
T4	43(1.1)
<b>N stage</b>	
N0	59 (20.8)
N1	121 (42.6)
N2	54 (19)
N3	50(17.6)
<b>Grade</b>	
I	107 (37.7)
II	130 (45.8)
III	47 (16.5)
<b>LVI</b>	
Negative	140(49.3)
Positive	144 (50.7)
<b>Operation Type</b>	
Breast Conservation (BCS)	213 (75)
Mastectomy	71(25)
<b>Relapse</b>	
No	204(71.8)
Yes	80(28.2)
Local	9(3.2)
Distant	71 (25)
<b>Chemotherapy Timing</b>	
Neoadjuvant chemotherapy	62(21.8)
Adjuvant chemotherapy	222(78.2)
<b>Adjuvant Radiotherapy</b>	
Yes	280(98.6)
No	4(1.4)

ER: Estrogen receptor, PR: Progesterone receptor, LVI: Lymphovascular Invasion

All patients were categorized into several age groups including 20 - 25 years, 26 -30 years, 31-35 years, and 36-40 years. After a median follow up of 68 (range, 36-156) months, 21 patients had died due to the disease. Most of the patients were in the age group of 36-40 years (53.9%) and identified with ductal histological type (95.1%), stage II (56.3%), T2 stage (61.6%), N1 stage (42.6%) and grade II (45.8%). The positive expression of the ER and PR along with negative expression of the HER2 receptor (ER+/PR+/HER2-) was observed in most of the patients (58.5%). Lymphovascular invasion (LVI) was observed

in almost half of the patients (50.7%). Totally, 75% of the breast cancer patients were treated with breast conservative surgery (BCS). Among all 80 patients who developed relapse, 9 (3.2%) and 71 (25%) had local and distant recurrence, respectively. Most of the patients received postoperative adjuvant chemotherapy (78.2%) and postoperative adjuvant radiotherapy (98.6%).

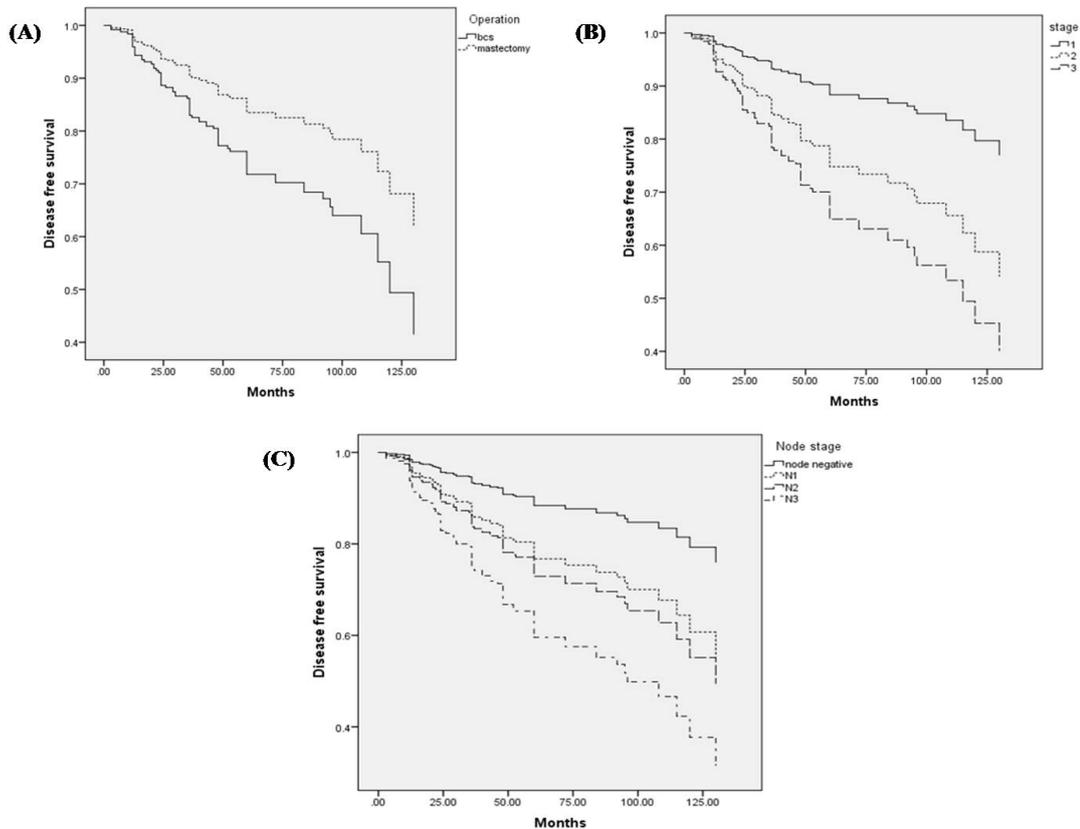
Evaluation of the potential association between baseline and clinicopathological features and DFS or OS was made using univariate Cox regression ([Table 2](#)).

**Table 2. Univariate Cox Regression Analysis of Disease- Free Survival and Overall Survival**

Parameters	DFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
<b>Categorized Age in Years</b>			0.281			0.513
20 to 25	1			1		
26 to 30	0.938	0.324-2.709	0.905	0.776	0.070-8.593	0.836
31 to 35	0.853	0.328-2.213	0.743	0.419	0.043-4.048	0.452
36 to 40	0.580	0.227-1.481	0.255	1.049	0.17-8.003	0.964
<b>Stage</b>			0.009			0.011
I	1			1		
II	2.511	1.133-5.565	0.023	1.179	0.245-5.682	0.837
III	3.508	1.522-8.081	0.003	3.959	0.882-17.759	0.072
<b>T Stage</b>			0.619			0.129
T1	1			1		
T2	0.997	0.578-1.720	0.990	1.207	0.326-4.460	0.778
T3	1.017	0.500-2.070	0.962	2.857	0.753-10.837	0.123
T4	2.517	0.583-10.865	0.216	5.158	0.527-50.492	0.159
<b>N Stage</b>			0.004			0.046
N0	1			1		
N1	2.301	1.013-5.226	0.047	2.422	0.512-11.464	0.265
N2	2.713	1.142-6.445	0.024	0.805	0.133-4.852	0.813
N3	4.215	1.799-9.879	0.001	3.917	0.831-18.470	0.084
<b>Grade</b>			0.894			
I	1			-		
II	1.009	0.626-1.626	0.970	-	-	-
III	1.170	0.598-2.291	0.646	-	-	-
<b>Operation Type</b>			0.019			0.832
Mastectomy	1			1		
Breast Conservation (BCS)	1.930	1.103-3.376		0.903	0.349-2.333	
<b>LVI</b>			0.622			0.674
Negative	1			1		
Positive	0.895	0.577 - 1.390		1.201	0.510-2.830	
<b>Hormone receptor Status</b>			0.083			0.906
ER+,PR+,HER2-	1			1		
ER-,PR-,HER2+	2.272	1.193-4.326	0.013	1.481	0.330-6.656	0.608
ER+,PR+,HER2+	1.606	0.859-2.999	0.138	1.389	0.391-4.939	0.612
ER-,PR-,HER2-	1.019	0.543-1.914	0.953	0.802	0.226-2.848	0.733

DFS: Disease Free Survival, OS: Overall survival, HR: Hazard Ratio, CI: Confidence interval, LVI: Lymphovascular Invasion, ER: Estrogen receptor, PR: Progesterone receptor

Low DFS was associated with stage II and stage III, as well as N1, N2, N3, Breast Conservation surgery, and ER-/PR-/HER2+ ( $p < 0.05$ ) (Figure 1).



**Figure 1.** Kaplan-Meier survival curves for young breast cancer patients categorized based on operation type (A), stage (B), and N stage (C) with  $P < 0.05$ . BCS: breast-conserving surgery

Low OS was also associated with stage III and N3 stage ( $p < 0.05$ ). Determination of the variable interactions which could affect survival was performed using multivariate Cox regression analysis. According

to this step, independent DFS predictive factors were BCS, stage II and stage III and also young age ( $p < 0.05$ ) (Table 3).

**Table 3.** Multivariate Cox Regression Analysis of Disease-Free Survival and Overall Survival

Parameters	DFS		
	HR	95% CI	P value
<b>Operation type</b>			0.002
Mastectomy	1		
Breast Conservation	2.567	1.425-4.624	
<b>Stage</b>			0.001
I	1		
II	2.703	1.161-6.291	0.021
III	4.868	0.050-11.56	0.000
<b>Categorized age in year</b>			0.055
20 to 25	1		
26 to 30	0.744	0.250-2.214	0.595
31 to 35	0.577	0.211-1.579	0.285

Parameters	DFS		
	HR	95% CI	P value
36 to 40	0.364	0.135-0.983	0.046

DFS: Disease Free Survival, HR: Hazard Ratio, CI: Confidence Interval

## Discussion

Despite the low incidence of breast cancer in young women, it is considered as a clinically significant concern owing to its worse clinical outcome. Therefore, raising the knowledge about breast cancer in young women can contribute to improved patient management. According to the growing evidence, compared to older patients, young breast cancer patients face with more aggressive pathological features including the presence of LVI, grade 3 histology, absence of estrogen receptor (ER), and overexpression of the human epidermal growth factor receptor-2 (HER-2) oncogene (3, 4, 15). Therefore, young patients aged less than 40 years are found with the higher risk of loco-regional recurrence, distant metastasis, and death compared to older patients (16). Based on previous reports, a 5% rise in death risk was observed in patients aged < 35 years for every one-year reduction in age, whereas no such changes were observed in patients aged 35-50 years. Therefore, sharp increase of the death risk was reported in patients younger than 35 years (17). In consistence with previous reports our retrospective study described that low DFS was associated with higher stages (II, III, N1, N2 and N3) and ER-/PR-/HER2+ status. Low OS was also significantly associated with higher stages (II, N3).

Although there are similar managing principles for invasive breast cancer in both young and older women special considerations should be given to management and therapeutic protocols. Young patients are at higher risk of emotional and psychosocial problems and need proper support from medical and psychosocial multidisciplinary teams (18, 19). Regarding the quality of life, breast-conserving surgery is more favorable for most young women compared to mastectomy. However, in the young patients (aged <35 years) the risk of local recurrence after breast-conserving surgery is nine times higher than older patients (aged >60 years). Although we found a significant association between low DFS and breast conservation surgery (BCS), similar to previous reports (18), no negative impact on the OS was observed after conservative surgery in young women (aged ≤40 years). Our results confirm previous reports that age is an important factor affecting the breast cancer prognosis and there is a significant association between young age and low DFS. The limitation of our study is that the type of chemotherapy was not included in the analysis.

## Conclusion

Taken together, our findings confirm that despite lower incidence of breast cancer in young women,

worse outcomes in this age group make it a major concern. Therefore, it seems that screening is important to be considered in young women in order to diagnose breast cancer early in this high-risk age group and decrease the risk of mortality. Further studies may be helpful to find best management strategies for young breast cancer patients.

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## Conflict of Interest

The authors declare that they have no competing interests.

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